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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/754,775	01/04/2001	David J. Grainger	295.009US3	6351

7590 10/23/2006

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EXAMINER	
KIM, JENNIFER M	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 10/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/754,775	GRAINGER ET AL.	
	Examiner	Art Unit	
	Jennifer Kim	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *173-194,196-203,205-211 and 231* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *173-194,196-203,205-211 and 231* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/7/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 7, 2006 has been entered.

Action Summary

The Double Patenting rejection of claims 173-194,196-203, 205-211 and 231 provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 153-173 of copending Application No. 10/729,056 is being maintained for the reasons stated in the previous Office Action and the rejection is repeated in this Office Action.

The Double Patenting rejection of claims 173-194,196-203, 205-211 and 231 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 8 of U.S. Patent No. 6,410,587B1 is being maintained for the

reasons stated in the previous Office Action and the rejection is repeated in this Office Action.

The rejection of claims 173-181, 205-211 and 231 under 35 U.S.C. 103(a) as being unpatentable over Sawada et al. (Pharmacometrics, 1992) is being maintained for the reasons stated in the previous Office Action and the rejection is repeated in this Office Action.

The rejection of claims 182-194, 196-203, 205, 206 under 35 U.S.C. 103(a) as being unpatentable over Warri (Dissertation Abstracts International, 1993) hereby expressly withdrawn in view of Applicants' amendment.

Upon further consideration, additional rejection has been made in this Office Action.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 173-181, 183 and 208 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the "decreasing lipid accumulation" in claims 178 and 208 and "reducing diabetic retinopathy" in claim 183, does not reasonably provide enablement for the "**inhibiting" or "inhibits"** such disorders (i.e. lipid accumulation or diabetic retinopathy). The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

3. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, predictability of the prior art, state of the prior art and the amount of experimentation necessary. All of the **Wands factors** have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: All of the rejected claims are drawn to a therapeutic method comprising **inhibiting** lipid accumulation (inhibiting diabetic retinopathy) comprising administering a compound of formula (I). The nature of the invention is extremely complex in that it encompasses the **actual inhibition equating to a prevention** of lipid accumulation (inhibiting diabetic retinopathy) such that the subject treated with above compounds does not contract lipid accumulation, plaque formulation.

Breath of the Claims: The complex of nature of the claims greatly exacerbated by breath of the claims. The claims encompass **inhibition** of lipid accumulation (inhibiting diabetic retinopathy) in humans, which has potentially many different causes (i.e. many different mutations or combination of mutations, medical history, hereditary, diet). Each of which may or may not be addressed by the administration of the claimed compounds.

Guidance of the Specification: The guidance given by the specification as to how one would administered the claimed compounds to a subject in order to actually **inhibit/prevent** lipid accumulation in humans is minimal. All of the guidance provided by the specification is directed towards **treatment relating to decrease lipid accumulation** (inhibiting diabetic retinopathy) **rather than inhibition** of lipid accumulation in humans.

Working Examples: All of the working examples provided by the specification are directed toward the treatment of decreasing lipid accumulation (inhibiting diabetic retinopathy) rather than **inhibition equating** to **prevention** of such condition in humans.

State of the Art: While the state of the art is relatively high with regard to treatment relating to a decreased lipid accumulation in humans. (i.e. atherosclerosis), the state of the art with regard to **inhibition/prevention** of such disorders is underdeveloped. In particular, there do not appear to be any examples or teachings in the prior art wherein a compound similar to the claimed compounds was administered to a subject to **inhibit** development of lipid accumulation (inhibiting diabetic retinopathy) in humans.

Predictability of the Art: The lack of significant guidance from the specification or prior art with regard to the actual **inhibition/prevention** of lipid accumulation (inhibiting diabetic retinopathy) in human subjects with the claimed compounds makes practicing the claimed invention unpredictable in terms of **inhibition equating prevention** of lipid accumulation in humans.

The amount of Experimentation Necessary: In order to practice claimed invention, one of skilled in the art would have to first envision a combination of appropriate pharmaceutical carrier, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system for one of the claimed compounds and test the combination in the model system to determine whether or not the combination is effective for **inhibition/prevention** of lipid accumulation (inhibiting diabetic retinopathy) in humans. If unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regard to the **inhibition/prevention** of lipid accumulation in human with any compound, one of skill in the art would have to then either envision a modification of the first combination of pharmaceutical compound, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above, and test the system again. If again unsuccessful, which is likely given the lack of significant guidance form the specification of prior art regarding **inhibition/prevention** of lipid accumulation (inhibiting diabetic retinopathy) in humans with any compound, the entire, unpredictable process would have to be repeated until successful. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to **inhibit/prevent** the development of lipid accumulation (inhibiting diabetic retinopathy) in humans in a subject by administration of one of the claimed compounds.

Therefore, a method of **inhibiting (preventing)** lipid accumulation in claims 173 and 208 and a method involving **inhibiting** diabetic retinopathy in claim 183 administering formula I is not considered to be enabled by the instant specification.

Claim 231 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claim is directed to a genus of **small vessel disease** which encompasses a vast array of diseases that are associated with small vessels. The instant specification does not describe the specific requisite characteristic of the disease in order to determine exactly which are qualified as "small" vessel disease. Any vessels in the body are somewhat "small" and within the physiology of the human body. This instant specification therefore does not provide a basis for one of skill in the art to envision the physical/functional characteristics of such a vessels involved in the "small vessel disease". Given this lack of description of sufficiently representative species encompasses by the genus of the claim the specification fails to sufficiently describe the claimed invention is such full, clear, concise, and exact term that a skilled artisan would recognize that Applicants were in possession of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 231 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "small vessel disease" in claim 231 is indefinite because it is not clear what are the diseases that are actually qualified as the "small vessel disease". One of ordinary skill in the art could not ascertain and interpret the metes and bounds of the term "small vessel disease" since it is not clear how small vessel involving the diseases are intended.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 173, 174, 178-183, 186-191, 196-201, 205-208, 210, 211 and 231 are rejected under 35 U.S.C. 102(b) as being anticipated by Nuovo et al. (1989).

Nuovo et al. teach administration of tamoxifen for treatment of endometrial polyps in postmenopausal patients with features including **thick-walled blood vessels**. (abstract).

That applicant may have determined a mechanism of **increasing the level of TGF-beta** in a same mammal by which the active ingredient gives the pharmacological effect does not alter the fact that the compound has been previously used to obtain the same pharmacological effects which would result from the claimed method. The patient (at **risk of or afflicted** with vascular indication characterized by a decreased lumen vessel diameter), **condition (thick-walled blood vessels encompassing decreased lumen vessel diameter**) to be treated and the effect are the same. An explanation of why that effect occurs does not make novel the same treatment of the conditions encompassed by the claims.

Claims 175-177, 184, 185, 192-194, 202, 203 and 209 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nuovo et al. (1989).

Nuovo et al. as applied as above.

Nuovo et al. do not teach the vivo results involves a mammal suffering diabetes, retinopathy, and the specified tamoxifen analogs set forth in claims.

It would have been obvious to one of ordinary skill in the art to employ tamoxifen analogs for the treatment of patients having endometrial polyps with thick-walled blood vessels in postmenopausal patients because Nuovo et al. teach that tamoxifen is useful for the treatment of patients afflicted or having risk of developing thick-walled blood encompassing decreased vessel lumen and because analogs have a viable utility and are homolog, isomers or close structural analogs of the claimed tamoxifen. The claimed compounds are so closely related structurally to the homologous; isomeric or analogous compounds of the reference as to be structurally obvious therefrom in the absence of

any unobvious or unexpected properties especially since one of ordinary skill in the art would expect that compounds so closely related structurally would have the same or essentially the same properties. With regard to treatment of the mammal having thick-walled blood vessels also suffering from the specified diseases set forth in claims is obvious because the effect of tamoxifen useful in treatment of endometrial polyps characterized by thick-walled blood vessel would not be effected by the concurrent medical condition including the diabetes and/or retinopathy.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 173-194,196-203, 205-211 and 231 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 153-173 of copending Application No. 10/729,056. Although the conflicting claims are not identical, they are not patentably distinct from each other because the

copending Application teaches an aspect of the claims in the instant application. For example, the method of claim 173 in the present application is similar to the method claimed in claim 153-173 utilizing same biological pathway comprising increasing the level of TGF-beta encompassing utilized same active agents. The copending application teaches the mechanisms of action or biological pathways presently claimed by Applicants and renders obvious the diseased claimed in the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 173-194,196-203, 205-211 and 231 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 8 of U.S. Patent No. 6,410,587B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent disclose and teach an aspect of the claims in the present application. For example the method of claim 173 in the present application is similar to the method claims in 6,410,587B1. The independent claim 173 in instant application is to a method of treating cardiovascular or vascular indication characterized by a decreased lumen diameter comprising administering formula (I) encompassed by formula (VI) of the patent. However, the effect is similar as to inhibiting lipid accumulation therefore renders Applicants' claims obvious.

Claims 173-181, 205-211 and 231 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sawada et al. (Pharmacometrics, 1992).

Sawada et al. teach the administration of toremifene citrate (NK622) in 0.1 mg/kg or more including 10mg/kg (cytostatic dose) to female rats showed decrease in total cholesterol in rats.

Sawada et al. do not teach a mammal at risk of or afflicted with cardiovascular or vascular indication (atherosclerosis) or mechanism of increasing the level of TGF-beta to decrease lesion formation or inhibition of lipid accumulation, and dosage formulation and the employment of analogs set forth in claim 176.

It would have been obvious to one of ordinary skill in the art to employ toremifene citrate (NK622) in 0.1 mg/kg or more including 10mg/kg (cytostatic dose) to a mammal at risk or afflicted with cardiovascular or vascular indication such as atherosclerosis. One would have been motivated to employ toremifene citrate (NK622) in 0.1 mg/kg or more including 10mg/kg (cytostatic dose) to a mammal at risk or afflicted with cardiovascular or vascular indication such as atherosclerosis because Sawada et al. teach the administration of toremifene citrate (NK622) in 0.1 mg/kg or more including 10mg/kg (cytostatic dose) to female rats showed decrease in total cholesterol in rats. One would be further motivated to make such a modification in order to achieve an expected benefit of lowering total cholesterol level in a mammal suffering from atherosclerosis. The pharmaceutical forms, e.g., sustained release, immediate release etc; mode of

administration, flavors, surfactant are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration. Further, the reference discloses compounds which have a viable utility and are homologs, isomers or close structural analogs of the claimed compounds. The claimed compounds are so closely related structurally to the homologous; isomeric or analogous compounds of the reference as to be structurally obvious therefrom in the absence of any unobvious or unexpected properties especially since one of ordinary skill in the art would expect that compounds so closely related structurally would have the same or essentially the same properties. That applicant may have determined a mechanism by which the active ingredient gives increasing the level of TGF-beta to decrease lesion formation or inhibition of lipid accumulation does not alter the fact that the compound has been previously used to obtain the same pharmacological effects (lowering total cholesterol) which would result from the claimed method upon the administration of same active agent in a same amount to the mammal in need thereof. An explanation of why that effect occurs does not make novel or even unobvious the treatment of the conditions encompassed by the claims.

Claims 182-194, 196-203, 205, 206 rejected under 35 U.S.C. 103(a) as being unpatentable over Warri (Dissertation Abstracts International, 1993).

Warri teaches the cellular and molecular mechanism of toremifene involving enhanced mRNA expression of TGF-beta in vitro and in vivo in breast cancer. Warri

teaches the growth of breast cancer is inhibited by a new antiestrogen toremifene. (abstract).

Warri does not teach the vivo results involves a mammal suffering diabetes, retinopathy, the effective amounts, and the analogs set forth in claim 202.

It would have been obvious to one of ordinary skill in the art to employ toremifene in a mammal to increase the level of TGF-beta. One would have been motivated to make such a modification because increasing the level of TGf-beta in vivo by toremifene taught by Warri reduces breast cancer. One would have been motivated to increase the level of TGF-beta by employing toremifene in order to achieve an expected benefit of treating breast cancer in mammal in any population including the patients having any other multiple disorders including diabetes, retinopathy.

For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 35 U.S.C. 103.

None of the claims are allowed.

Response to Arguments

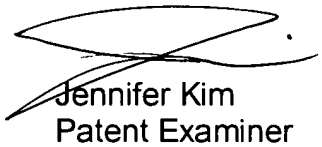
Applicants' arguments filed August 7, 2006 have been fully considered but they are not persuasive. Applicants argue that there is insufficient suggestion or motivation to modify Sawada to reach the present invention because the decrease in cholesterol is

part of a general toxic syndrome arising from higher than appropriate dosage of toremifene which corresponds with suppressed weight gain and a drop in feed consumption. This is not persuasive because instant claims are drawn to "cytostatic dose" of a therapeutic agent (i.e. claim 173) and "effective amount" of treating "arteriosclerosis . . ." (i.e. claim 231). Therefore, the teaching of Sawada that the dose administered to "decrease in cholesterol" encompasses the "cytostatic dose" and "effective amount" to treat arteriosclerosis. It is noted that Sawada's "higher than appropriate dosage of toremifene" asserted by Applicants' still reads within the claimed dosage limitation as "cytostatic" and "effective". Applicants argue that based upon the disclosure of Sawada, it is unclear whether the reduction in total cholesterol is due to the action of toremifene on TGFb levels, whether it is due to the toxicity of toremifene, or if it is due to the decrease in feed consumption. This is not persuasive because the teaching of Sawada is clear that the effect of decrease in total cholesterol is resulted of orally administered NK622 (toremifene). Applicants' attention is drawn to second paragraph of abstract of Sawada where it states "This experiment yielded the following results... showed decreases in total cholesterol, phospholipid and total protein values in rats receiving 0.1mg/kg or more...".

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Kim whose telephone number is 571-272-0628. The examiner can normally be reached on Monday through Friday 6:00 am to 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Jennifer Kim
Patent Examiner
Art Unit 1617

Jmk
October 13, 2006